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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GABEL, GAILENE	

ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,345	RITCHLIN ET AL.	
	Examiner	Art Unit	
	GAILENE R. GABEL	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-93* is/are pending in the application.

4a) Of the above claim(s) *7-11,17-20,32,41-44 and 46-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,12-16,21-31,33-40 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-93* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 March 2004 and 24 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/25/05; 9/12/05; 11/28/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group I, claims 1-31, 33-45 and 49, with traverse, filed February 11, 2008, is acknowledged and has been entered. Claims 32, 46-48, and 50-93 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected invention.

Applicant also elected the following patentably distinct species for examination on the merits:

A) Marker - CD11b;

B) Selected number of markers - At least one marker recited in claim 3, 13, and 36;

C) Sample – Blood recited in claim 16;

D) Method of measurement – FACS recited in claims 21 and 37.

Upon further consideration of the restriction requirement, however, Examiner determined that claims 4-6, 14, and 38-40 drawn to patentably distinct species, can be rejoined for examination and prosecution on the merits. Claims 4-6 and 38-40 are drawn to at least two, at least three, and at least four; claim 14 is drawn to Immunochemistry detection; and claims 4-6 and 38-40 are drawn to CD14, CD51, and RANK as cell surface markers. Accordingly, claims 7-11, 17-20, and 41-44 are also withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being claims drawn to a non-elected species.

Accordingly, claims 1-93 are pending. Claims 1-6, 12-16, 21-31, 33-40, and 45 are under examination.

2. Applicant traverses the restriction requirement on the grounds that serious burden would result if all the claims are examined together.

In response, Examiner determined that claims 4-6, 14, and 38-40 can be rejoined for examination and prosecution on the merits. In as far as Applicant's contention that Examiner has not established serious burden in examining all the claims together, it is maintained that literature search for each method is distinct since the structural requirements of each invention are different, rendering search for relevant art and examination of all claims burdensome. While searches would be expected to overlap, there is no reason to expect the searches to be coextensive. Accordingly, the restriction requirement is being maintained.

Information Disclosure Statement

3. The listing of references in page 132-147 in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

4. The information disclosure statement filed February 25, 2005 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent or publication listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. In this case, reference A74 (Kaposi et al.) has not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3, 11-13, 15, 16, 21-31, 33-37, and 45 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In this case, claim 1 recites a method of diagnosing a subject with inflammatory joint disease (IJD) by measuring how many osteoclast precursor cells (OCP) are in the blood of the subject. However, claim 1 fails to specifically recite a correlation step that correlates what number or threshold levels are required in order to define an indication of IJD.

Claim 2 is indefinite in reciting, "PBMC". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 2 is ambiguous in reciting, "further comprising collecting the subject's PBMC" because it is unclear what essential structural cooperative relationship exists between the collecting step in claim 2 and the measuring step in claim 1 from which it depends. Does Applicant intend collecting the subject's PBMCs first and therefrom, measuring the number of OCPs.

Claim 15 is indefinite in reciting, "TRAP". Acronyms or abbreviations must be fully defined and recited at least one time in a set of claims.

Claim 15 is ambiguous in reciting, "counting how many multinucleated cells there are producing a number of multinucleated cells in the sample." Please clarify and correct accordingly.

Claim 15 is ambiguous in reciting, “more” because "more" is a relative term which lacks a comparative basis for defining its metes and bounds. The term "more" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 25 is confusing in its intended scope in reciting, “wherein the disease is PsA or RA, aseptic joint loosening of orthopedic implants, non-nion of a fracture, spondyloarthropathies, psoriasis and Crohn’s Disease” because it does not specifically and clearly define what specific IJD is being detected or diagnosed. It appears that the disease intended to be detected is either PsA or RA in a closed language; however, subsequent recitation of “joint loosening of orthopedic implants, non-nion of a fracture, spondyloarthropathies, psoriasis and Crohn’s Disease” appears to improperly open up the claim to other diseases that can be detected.

Claim 26 is incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. In this case, claim 1 recites a method of diagnosing a subject with inflammatory joint disease (IJD) by culturing peripheral blood mononuclear cells and then assaying the number of osteoclasts formed. However, claim 26 fails to specifically recite a correlation step that correlates what threshold levels of osteoclasts are required from the assay in order to define an indication of IJD.

Claim 29 is ambiguous in reciting, “increased” because "increased" is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be relative to a healthy control subject. The term "increased" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 31 is objected to in reciting, “PBMA”. Perhaps, Applicant intends, “PBMC.”

Claim 33 is indefinite in reciting, “more” because "more" is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a control subject. Specifically, claim 33 fails to specifically define what threshold levels of OCP, i.e. how much more, are required to be measured in order to determine the presence of IJD. Additionally, claim 33 fails to make clear as to whether the control should be a normal (healthy) control of an abnormal control. Lastly, the recitation of “[presence of] disease” lacks clear antecedent basis.

Claim 36 recites improper Markush language in reciting, “selected from the group consisting of … and or….” Change to “selected from the group consisting of … and....” for proper Markush language.

Claim 45 is indefinite in reciting, “more” because "more" is a relative term which lacks a comparative basis for defining its metes and bounds, albeit recited to be comparative to a healthy control subject. Specifically, claim 33 fails to specifically define what threshold levels of OCP, i.e. how much more, are required to be measured in order to provide indication of IJD.

Double Patenting

6. Claims 1-3, 12-16, 21-26, and 33-36 of this application conflict with claims 1-3, 11-13, 15, 16, 21-26, 33-36 of Application No. 10/548,389. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may

obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

7. Claims 1-3, 12-16, 21-26, and 33-36 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1-3, 11-13, 15, 16, 21-26, 33-36 of Application No. 10/548,389. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

8. Claims 1-3, 12-16, 21-26, and 33-36 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-3, 11-13, 15, 16, 21-26, 33-36 of copending Application No. 10/548,839. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. Claims 1-6, 12, 14, 21-28, 30, 34-36, 38-40, and 49 are rejected under 35 U.S.C. 102(a) as being anticipated by Hirayama et al. (Osteoclast formation and activity in the pathogenesis of osteoporosis in Rheumatoid Arthritis, Rheumatology 41: 1232-1239 (2002)).

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Hirayama et al. provide that Rheumatoid Arthritis (RA) is manifested as increased bone resorption by osteoclasts; hence, analyzed osteoclast formation from circulating precursors in RA patients (see Abstract). According to Hirayama et al., RA patients show bone erosion on radiograph which is manifested as lower bone mineral density (p. 1232, col. 1). In practice, Hirayama et al. teach collecting blood sample from patients and normal subjects into heparinized tubes. Thereafter, peripheral blood mononuclear cells (PBMC) are collected and isolated by allowing them to settle in Ficoll-Hypaque gradient centrifugation. The PBMC cell preparations were fixed and stained histochemcally for tartrate resistant acid phosphatase (TRAP) and immunohistochemically with monoclonal antibody against CD14. The number of stained multinucleated TRAP positive cells were counted and compared to normal control samples, so as to provide indication of osteoclast formation in RA patients. Hirayama et al. teach culturing the PBMCs with or without exogenous addition of M-CSF and RANKL (p. 1233, cols. 1 -2). According to Hirayama et al. osteoclasts are specialized multinucleated cells which carry out bone resorption; they are formed from mononuclear precursors that circulate in the monocyte fraction of peripheral blood. These mononuclear precursors express the monocyte/macrophage antigens CD11b and CD14, and are entirely negative for phenotypic markers for osteoclasts including TRAP and entirely lack the ability to carry out bone resorption. It has been shown, however, that CD14 positive cells in the monocyte fraction which express the receptor activator nuclear factor kB (RANK), can differentiate into functional osteoclasts in the presence of cells that express macrophage colony-stimulating factor (M-CSF) and RANK ligand including osteoblasts (p. 1232, col. 2 – p. 1233, col.1).

10. Claims 1-5, 12, 14, 21, 23-28, 34-36, 38, and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Jevon et al. (Osteoclast formation from circulating precursors in Osteoporosis, Scand J Rheumatol 32: 95-100 (January 1, 2003)).

Jevon et al. provide that there is imbalance between bone formation and bone resorption that underlie the pathogenesis of reduced bone mass in osteoporosis; hence aim to determine the role of osteoclast formation using patients having bone and joint disorders. According to Jevon et a., bone resorption is carried out by osteoclasts which are formed from marrow-derived cells that circulate in the monocyte fraction. In practice, Jevon et al. teach collecting blood sample from patient and normal subjects and isolating peripheral blood mononuclear cells (PBMC) by allowing them to settle in gradient centrifugation (Abstract and p. 95, col. 2 - p. 96, col. 1). The cell preparations were fixed and stained histochemcally for tartrate resistant acid phosphatase (TRAP) and immunohistochemically with monoclonal antibody against CD14 and CD51. The number of stained multinucleated TRAP positive cells (TRAP activity) containing three or more nuclei were counted and compared to normal control samples so as to provide indication of osteoclast formation. Jevon et al. teach culturing the PBMCs with or without exogenous addition of M-CSF (p.96, col. 2).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims13, 15, 16, 29, 31, 33, 36, 37, and 45 rejected under 35 U.S.C. 103(a) as being unpatentable over Hirayama et al. (Osteoclast formation and activity in the pathogenesis of osteoporosis in Rheumatoid Arthritis, Rheumatology 41: 1232-1239 (2002)) in view of Li et al. (Systemic TNFa Promotes Erosive Bone Resorption by Increasing the Number of CD11b+ Osteoclast Progenitors in the Periphery which are Dependent on RANK Signaling of Osteoclastogenesis, Journal of Bone and Mineral Research: JBMR Program and Abstracts (2002)).

Hirayama et al. differ from the claimed invention in failing to teach detecting and analyzing CD11b by fluorescence activated cell sorting (FACS).

Li et al. teach that TNFa is a potent osteoclastogenic factor shown to act directly on cells in osteoclast lineage, or indirectly by affecting the production of the essential osteoclast differentiation factor RANKL by osteoblasts. Li et al. studied the effect of chronic TNFa exposure to osteoclast precursor (OCP) differentiation and the requirement of RANK/RANKL in the process and found that the number and frequency of OCP expressing CD11b is increased. OCP cells expressing CD11b are detected and sorted using FACS. Li et al. suggested that CD11b may be used as marker of osteoclast progenitors.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Li into the method of Hirayama and detect CD11b cells using FACS to analyze

CD11b expression in the OCPs because FACS is well-known in the art for its multiparametric detection capability and conventionally used for its accuracy in specifically identifying and separating cells based on cell surface antigen expression. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teaching of Li in increased expression of CD11b in OCP found in inflamed arthritic joints so as to be used as specific marker for OCP progenitors in IJD such as RA in the method of Hirayama because Hirayama found that OCPs correlate directly to increased osteoclast functional activity in RA whereupon inflamed arthritic joints manifest bone erosion surfaces; hence, providing fast accurate procedure in detecting OCPs in PBMCs of RA patients.

12. No claims are allowed.

Remarks

13. Prior art made of record are not relied upon but considered pertinent to the applicants' disclosure:

Gregoretti et al. (Osteoclast precursors circulate n the peripheral blood of patients with aggressive multiple myeloma, Leukemia 9: 1392-1397 (1995)) teach that patients with aggressive MM have a population of circulating osteoclast precursors which may contribute to generalized bone erosion observed in MM patients. The cells are characterized as multinucleated, TRAP positive, and are observed to express CCD14 (Abstract and p. 1394, col. 2).

Massey et al. (Human Osteoclasts derive from CD14 positive monocytes, British Journal of Hematology 106: 167-170 (1999)) teach identifying the phenotype of osteoclast precursors. Massey et al. provide that osteoclasts are CD14- and CD11b- but confirmed that co-culturing PBMCs with osteoblastic UMR 106 cell line resulted to osteoclast co-expression of CD14 and CD11b (Abstract).

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GAILENE R. GABEL whose telephone number is (571)272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/GAILENE R. GABEL/
Primary Examiner, Art Unit 1641

April 24, 2008